REMARKS

In the Office Action dated July 7, 2009, Claims 1-17 and 20-27 were pending. Claims 21-25 were withdrawn from further consideration as directed to non-elected subject matter. Claims 1-17, 20, 26 and 27 are examined to the extent that the claims read on the combination of connexin 26, pendrin, mitochondrial 12s rRNA and usherin, and on SEQ ID NO: 1. Claims 1-17 and 20 are objected to because they specifically recite non-elected subject matter. Claim 1 is also objected to for containing typographical errors. Claims 1-15, 17 and 20 are rejected under 35 U.S.C. §112, second paragraph, as indefinite. Claims 1-17, 20, 26 and 27 are also rejected under 35 U.S.C. §103(a) as allegedly unpatentable based on various combinations of prior art references.

This Response addresses each of the Examiner's rejections and objections. Applicants therefore respectfully submit that the present application is in condition for allowance. Favorable consideration of all pending claims is therefore respectfully requested.

Substance of Telephone Interview

A telephone interview was conducted on August 10, 2009 between the undersigned attorney and the Examiner. During the interview, the current election and the possibility of a claim based on the combination of SEQ ID NOS: 33-64 being examined were discussed. The Examiner indicated that such a claim would be considered as directed to non-elected subject matter and would not be considered. The Examiner acknowledged that she would consider and examine such a claim upon filing of a Request for Continued Examination (RCE).

Claim Amendments

Claims 1-25 have been canceled without prejudice in the instant amendment.

Claim 26 has been amended to further define the specific hybridization conditions. Support for such conditions is found in previous claim 1 and the specification, e.g., the bridging paragraph on pages 86-87. Claim 26 has also been amended to clarify that the hybridization conditions permit hybridization of single-stranded RNA or DNA which is exactly complementary to an immobilized allele specific oligonucleotide, "but substantially less or no hybridization of non-complementary single-stranded RNA or DNA molecules." Support for this amendment is found in original claim 1.

New claims 28-47 are added, essentially directed to the combination of SEQ ID NOS: 33-64 and use thereof in methods of genotyping. Specifically, claims 28-40 are directed to methods of genotyping a subject with respect to connexin 26, pendrin, mitochrondrial 12S rRNA and usherin based on hybridization to an array of oligonucleotides under specific conditions, wherein each of SEQ ID NOs: 33 to 64 is present in said array. Claims 41-45 are directed to a set of oligonucleotides, wherein each of SEQ ID NOs: 33 to 64 is present in said set. Claims 46-57 are directed to an array comprising a set of oligonucleotides, wherein each of SEQ ID NOs: 33 to 64 is present in said set.

Support for new claims 28-47 is found in original claims 1-25, particularly claims 16, 17 and 21, and throughout the specification. No new matter is introduced.

Applicants further respectfully submit that claims 28-47 correspond to the elected invention. Specifically, the method claims are directed to genotyping a subject with respect to the combination of the four genes: connexin 26, pendrin, mitochrondrial 12S rRNA and usherin.

Further, the new claims require the sequence of SEQ ID NO: 33, which is "included" within the elected sequence of SEQ ID NO: 1 (see Table 1 on pages 6-7 of the specification). Therefore, Applicants respectfully request that claims 28-47 be included in the examination. In the event that the Examiner considers these new claims to represent a non-elected invention, Applicants believe that based on the telephone interview, the Examiner will examine these claims upon the filing of an RCE (i.e., after receiving a Final Rejection should it issue).

35 U.S.C. §103(a) Rejections

The rejections and objections directed to claims 1-25 are moot in light of the cancellation of these claims. Applicants will now address the obvious rejections of claims 26-27.

Claim 26 is rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Kudo et al. (*American Journal of Medical Genetics* 90: 141-145, 2000) ("Kudo") in view of Smith (*Seminars in Pediatric Neurology* 8: 147-159, 2001), Sato et al. (*European Journal of Endocrinology* 145: 697-703) ("Sato"), Fischel-Ghodsian et al. (U.S. Patent 5,506,101) ("Fischel-Ghodsian"), Najera et al. (*Human mutation* 20: 76, 2002) ("Najera"), and Van Ness (U.S. Patent 5,994,065).

Kudo teaches genotyping of the connexin 26 gene for deafness by ASO hybridization. The Examiner admits that Kudo does not teach the specific hybridization constraints nor genotyping of pendrin, mitochondrial 12s rRNA and usherin. However, the Examiner has relied upon the additional cited art as follows. Smith teaches that connexin 26, pendrin, mitochondrial 12s rRNA and usherin are all associated with hearing loss, including specific mutations in connexin 26 and mitochondrial 12s rRNA. Sato teaches that the missense mutation H723R in the pendrin gene is associated with hearing loss, and further teaches genotyping the mutation

based on allele-specific PCR. Fischel-Ghodsian teaches detecting 12s rRNA gene mutations associated with deafness, using an ASO hybridization technique. Najera teaches mutations of the usherin gene that are associated with hearing loss and detection of these mutations by performing an SSCP analysis. Van Ness teaches a method for hybridization which reduces the non specific background. According to the Examiner, Van Ness teaches the hybridization constraints of the instant claims. The Examiner contends that the ordinary artisan would be motivated to perform routine optimization of the method of Kudo et al. and use the hybridization constraints of Van Ness in order to reduce hybridization backgrounds with a predictable expectation of successful hybridization due to the functional similarities of the washing conditions of Kudo et al. and Van Ness.

Applicants respectfully disagree with the rejection and submit the following.

Claim 26, as amended, is directed to genotyping a subject using hybridization with a panel of allele specific oligonucleotides covering a mutation in each of four specific genes, namely connexion 26, pendrin, mitochondrial 12s rRNA and usherin. The panel of allele-specific oligonucleotides and the specified hybridization conditions are designed to distinguish between single-stranded nucleic acid molecules such that only molecules that are exactly complementary to the allele specific oligonucleotide anneal under the recited hybridization conditions. A key feature of the claimed method is that the method achieves genotyping of four genes and simultaneous detection of mutations in each of the four genes using an array under a single set of hybridization conditions. The allele specific oligonucleotides in the panel are designed to permit hybridization of single stranded nucleic acid molecules under a single set of hybridization conditions, and the hybridization conditions are such that permit differential hybridization between identically complementary nucleotide sequences and those which differ by

a single nucleotide, thereby identifying polymorphisms in each of the four genes in the subject's genome.

The ability of the claimed method to detect multiple mutations in a single hybridization assay in an array format is demonstrated in the present specification, e.g., Example 6 (page 93), whereby the presence or absence of two connexin mutations is detected simultaneously; and Example 7 (page 94), which shows the genotyping of four pendrin mutations, together with the 12S rRNA mutation.

While the cited references appear to have taught the association of the four genes with hearing loss and the detection of certain mutations in these genes, these references do not teach a method that is capable of determining mutations in all four genes using a single test, as presently claimed.

In fact, the cited references evidence the use of different methodologies in detecting mutations. Specifically, Kudo and Fischel-Ghodsian teach allele specific oligonucleotide hybridization ("ASO"), Sato teaches allele specific PCR, and Najera teaches SSCP analysis, for detecting certain mutations. Smith only presents a general discussion of the genes and mutations associated with hearing loss without discussing the techniques for detecting the mutations. Van Ness is simply directed to hybridization techniques in general for reducing non-specific background, without addressing any specific mutations in any of the four genes recited in the claims.

Therefore, the cited references, taken singularly or in combination, simply do not suggest or provide a motivation for those skilled in the art to devise *a single array hybridization test* in order to detect mutations in all four genes. Each mutation would require a separate analysis based on distinct technologies as taught by the references. Further, the cited references

would not have provided any reasonable expectation of success in devising *a single array hybridization test* for detecting mutations in all four genes.

Accordingly, it is respectfully submitted that the method as presently recited in claim 26 is not obvious based on the combination of the cited references, and represents a tremendous improvement over the prior art methodologies. Withdrawal of the rejection is therefore respectfully requested.

Claim 27 is rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Kudo, Smith, Sato, Fischel-Ghodsian, Najera and Van Ness, as applied to claim 26 above, and further in view of Dobrowolski et al. (U.S. Published Application 2004/0038266).

The Examiner acknowledges that the combination of Kudo, Smith, Sato, Fischel-Ghodsian, Najera and Van Ness does not teach a method of genotyping connexin 26 wherein the oligonucleotide comprises SEQ ID NO: 1. However, the Examiner refers to Dobrowolski, which allegedly teaches a method of screening for hearing loss by detection of connexin 26 mutations using the sequence of SEQ ID NO: 1.

Applicants reassert that the combination of Kudo, Smith, Sato, Fischel-Ghodsian, Najera and Van Ness fails to teach or suggest the features recited in independent claim 26, as discussed above. Dobrowolski does not cure the deficiencies of the combination of Kudo, Smith, Sato, Fischel-Ghodsian, Najera and Van Ness. Therefore, dependent claim 27 is also unobvious over the cited combination of references. Withdrawal of the rejection of claim 27 is therefore respectfully requested.

Conclusion

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

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